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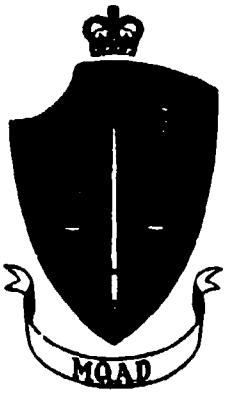

MQAD REPORT No. 262

CHARACTERISATION OF NITROCELLULOSE BY GEL PERMEATION CHROMATOGRAPHY PART 1 TECHNIQUE AND CALIBRATION

by

D E Hillman and J I Paul

MATERIALS QUALITY ASSURANCE DIRECTORATE
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The 3-hydroxy derivatives of fentanyl, known metabolites of fentanyl, have been synthesized in diastereomerically pure form. These syntheses, which begin with epoxide opening by aqueous aniline, incorporate a novel cyclization-cleavage sequence that makes isomer separation possible.

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PREFACE

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CONTENTS

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METABOLITES OF THE FENTANYL FAMILY. SYNTHETIC STUDIES ON THE 3-HYDROXY DERIVATIVES

1. INTRODUCTION

Fentanyl is a potent synthetic opioid that has a potency of almost 300 times that of morphine in rat tail withdrawal tests. This finding was particularly interesting because it allowed one to test the postulate[1] that highly potent opioids owe their activity to their enhanced ability to discriminate between the receptors for opioid analgesia (μ-receptors) and those that give rise to the undesirable side effects of respiratory and cardiac depression, emesis, and dependence. Support for this concept was furnished by the finding that fentanyl has only minimal effects on the cardiac function, and accordingly, has been widely used in heart surgery procedures. The search for even more potent opioids has continued with the hope of discovering analgetics that are virtually free of side effects.

There is good reason for optimism in the search for compounds that elicit analgetic responses and produce minimal undesirable side effects. The fact that different opioids produce different distributions of physiological effects has been rationalized by the concept, first proposed by Martin and co-workers,[2] that different drugs interact to varying degrees with multiple opiate receptors; subsequent research has provided compelling support for this theory. It is generally believed that there are five receptor subtypes. The μ-receptor is the prototypical morphine receptor involved with graduated indifference to painful stimuli and the environment in general. The δ- and ε-receptors specifically bind the endogenous peptides enkephalins and β-endorphin, respectively. Sedation and spinal nociceptive responses are the function of the κ-receptor; ketocycloazocine and its ethyl derivative are typical agonists. The σ-receptor has little or no antinociceptive activity but is believed to be responsible for the psychotomimetic actions of the opioids.

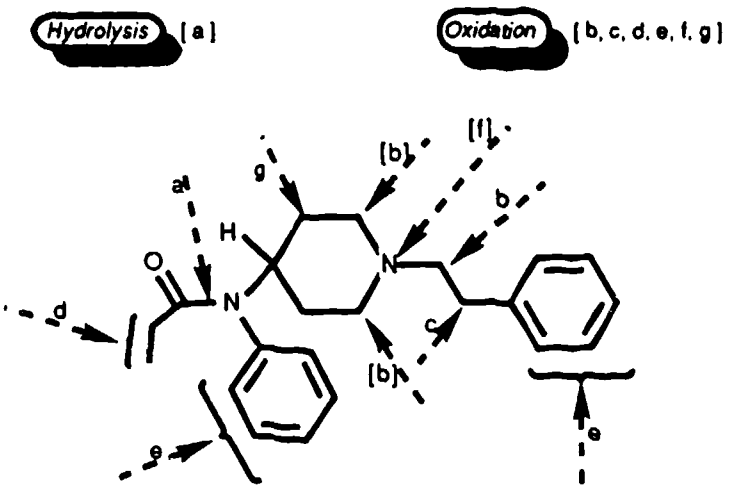
Recent studies by Pasternak and Wood,[3] based on the use of very high specific activity ^{3}H-labelled naloxone and dihydromorphine, suggest that there are two μ-receptors, μ_1 and μ_2. The μ_1-receptor has a very high affinity for opioids and is responsible for supraspinal analgesia with no peripheral actions. The receptor has a lower binding capacity, however, accounting for a relatively small proportion of the total specific binding. In mice and rats, the μ_2-receptor was found to bind to those regions of the central nervous system (CNS) that are known to be intimately involved in antinociception. The lower affinity μ_2-receptor is implicated in respiratoryand cardiovascular depression and in physical dependence. It should be possible to find molecules, which interact minimally with the μ_2-receptor.

We have been interested in exploring the possible influence of the metabolites of fentanyl on its activity and side effects.[3] Encouragement to pursue this investigation was provided by the results of Nordberg and co-workers,[4] who found that metabolites of meperidine had more antinociceptic activity and diminished respiratory depressive effects than the parent drug when administered by the intracerebroventricular route.

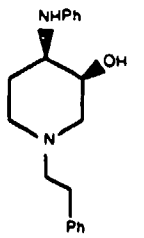
Fentanyl is a polyfunctional molecule that has many possible hydrolytic and oxidative pathways (Scheme I). The products of most of these metabolic pathways have been observed in mammalian species; pathways whose products have not been reported in the literature are in brackets. Banks and Ferguson[5] found that those metabolites of fentanyl that had been studied were found to be inactive. These findings were not unexpected because

administration of these relatively polar metabolites was either by an intravenous or intramuscular route. It appeared unlikely that these metabolites would be lipophilic enough to pass through the blood-brain barrier and interact effectively with the μ-receptors of the CNS. As a result of the recent discovery of active meperidine metabolites[4] and interest in the brain as a metabolic site,[6] the authors suggest that it would be more appropriate to assess the activity of fentanyl metabolites by means of opioid receptor binding studies, followed by experiments employing intracerebroventricular administration, if significant binding were to be discovered.

Scheme I



Of the reported fentanyl metabolites,[3] those bearing a 3-hydroxy substituent promised to be particularly interesting. This interest was occasioned by the possibility that 3-substituents other than methyl result in enhanced pharmacological activity and by the fact that the chemistry of the hydroxy group can be exploited for the preparation of many derivatives for pharmacological testing. The preparation of pure samples of *cis*- and *trans*-1-(2-phenylethyl)-3-hydroxy-4-phenylamino-piperidine (**1** and **2**), immediate precursors to the propanamide metabolites identified by Goromaru,[7] is described.



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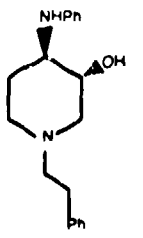

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2. DISCUSSION AND RESULTS

A direct route from the 1,2,3,6-tetrahydropyridine derivative is suggested by the work of Barluenga and co-workers[8] who treated acyclic and cyclic alkenes with mercury(II)

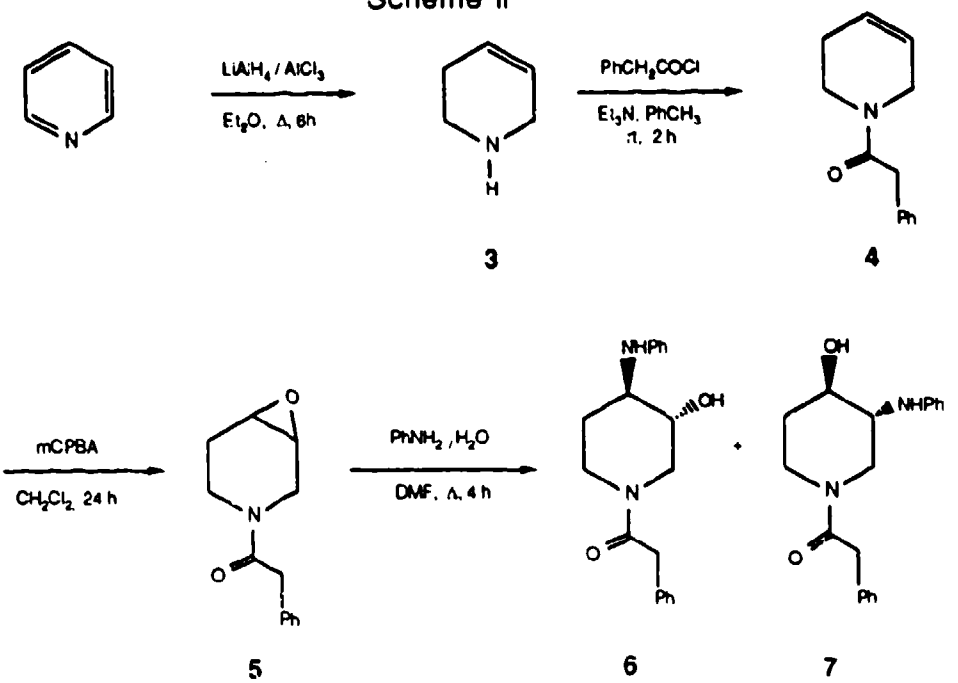
oxide/tetrafluoroboric acid and aniline in tetrahydrofuran at -10 °C. Good yields of the 2-anilinoalcohols were obtained with predictable, high regioselectivity and trans stereospecificity. No results are provided for heterocyclic compounds. Herrant and Sharpless and Dubey and Knans[9,10] report the vicinal oxyamination of alkenes in fair to good yield using osmium-catalyzed processes; modification of this chemistry for the preparation of anilino derivatives would not be straightforward. Other methods focus on the opening of epoxides. The use of the strongly basic PhNHMgBr,[11] $PhNHAlEt_2$,[12] or aniline at 100 °C using catalytic Al_2O_3[13] was discounted in favor of the considerably milder aqueous aniline system described below.

The approach that seemed most reasonable in view of the required heterocylic backbone was cleavage of epoxide **5**. This route is fraught with regio- and stereoselectivity problems. Achieving high regioselection in epoxide cleavage appeared to be unlikely because the only feature of the molecule that renders C_3 and C_4 different is the relatively distant ring nitrogen that is, due to its unshared pair of electrons, unlikely to be involved under nucleophilic, essentially neutral conditions.

If the reaction is run under S_N2 conditions, exclusive formation of *trans* diastereomers is demanded. The source of the *cis* diastereomer is then necessarily the *trans* isomer. Provided that the separation of *cis* and *trans* isomers was relatively easy (as it turned out to be in the present study), the method for inversion of configuration need not be completely stereoselective. One method of bringing this about might be to change the conditions for epoxide opening from S_N2 to S_N1. In this reactant-like transition state, the symmetrical carbocationic intermediates (at C_3 and C_4) should be attacked with equal facility. The synthetic approach for *trans*-1-phenylacetyl-3-hydroxy-4-phenylamino-piperidine (**4**) is shown in Scheme II. Reduction of pyridine using lithium aluminum hydride in the presence of aluminum chloride following the procedure of Ferles[14] yielded 1,2,3,6-tetrahydropyridine (**3**). Acylation of crude **3** with phenylacetyl chloride produced amide (**4**). Epoxidation with m-chloroperbenzoic acid provided epoxide **5**, which could be cleaved with aniline in aqueous dimethylformamide (DMF) to provide a 1:1 mixture of regioisomers **6** and **7**, identified by the downfield shift of the C_2 protons of **6** relative to those of **7** in the ^1H NMR spectra. Fortunately, desired isomer **6** could be easily obtained from the mixture by chromatography. Reduction of **6** with $LiAlH_4$ smoothly converted **6** to **2**.

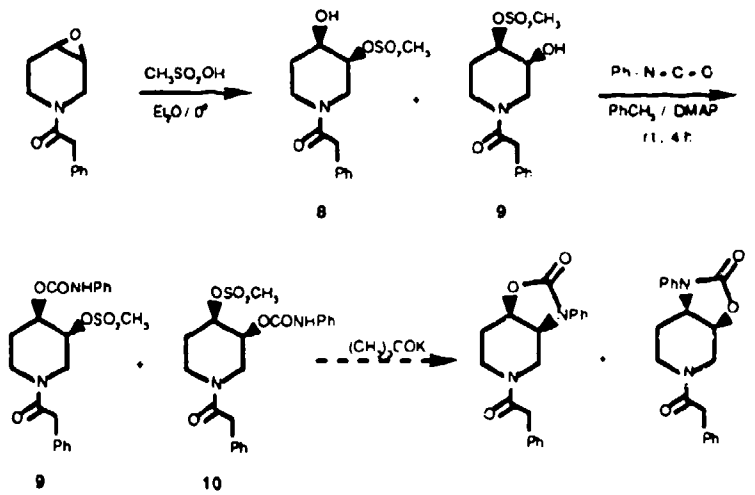
To obtain metabolite **1**, methods for inversion of configuration at C_3 were explored. A reasonable approach that was anticipated to produce a mixture of *cis* and *trans* isomers was oxidation of **6** to the corresponding ketone, followed by hydride reduction of the carbonyl function. If the transition state in the reaction is early, the product composition should reflect the differences in energy of the two paths for approach of the hydride reducing agent (from above or below the plane of the carbonyl moiety.) Because approach from above, producing *cis*-anilinoalcohol **1**, should be less hindered than the case for cyclohexane (one of the *syn*-axial hydrogens has been replaced by the delocalized nitrogen lone pair), the steric hindrance offered by the bulky 4-anilino function should be the major factor in determining the direction of attack. The predominant product of the reaction, using this first-order analysis, which ignores interaction of the reducting agent with other functionalities in the molecule and the role of polymeric species, should be *cis*-anilinoalcohol **1**, arising from approach of the hydride reducing agent from that face opposite to the anilino function. Unfortunately, when Swern conditions[15] were used to oxidize the hydroxy function and $LiAlH_4$ was used to reduce the resulting ketone, only *trans* isomer **2** was obtained. The assignment of relative stereochemistry was confirmed by formation of **2** by $LiAlH_4$ reduction of **6**.

Scheme II



A second approach is outlined in Scheme III. Epoxide **5** was treated with methanesulfonic acid producing *trans* regioisomers **8** and **9**. Although preparation of phenylurethanes **9** and **10** was straightforward, attempts to generate the oxazolidones by treating the mixture with KOtBu were unsuccessful.

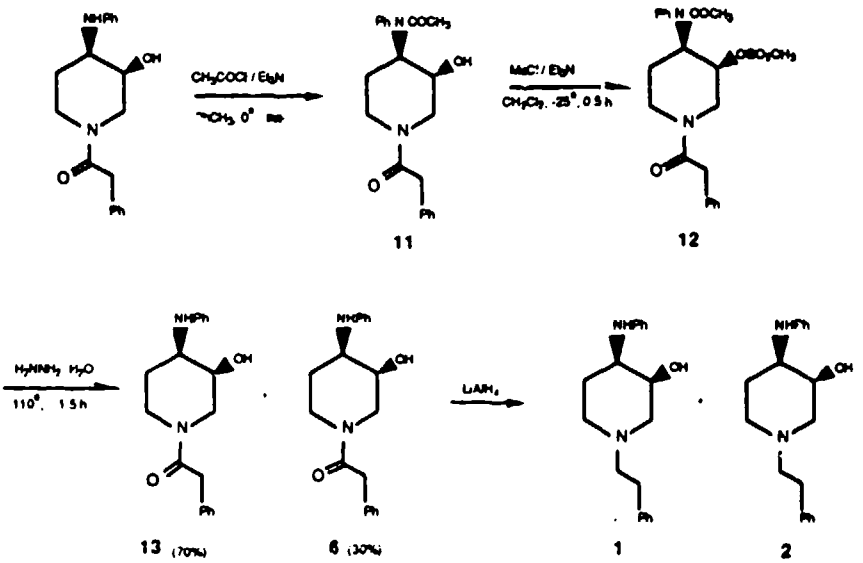
Scheme III



The preparation of a mixture of **1** and **2** from which **1** could be readily separated by chromatography is shown in Scheme IV. The key step in the synthesis was application of the method of Lier[16] to mesylate **12**. The overall reaction proceeded with predominant

inversion of configuration at C_3. Chromatographic separation of diastereomers proved to be more convenient following $LiAlH_4$ to the final products.

Scheme IV



3. CONCLUSIONS

Methods for preparation of **1** and **2** from pyridine have been developed. While *trans* isomer **2** was obtained with relative ease, the *cis* isomer was prepared in lower yield by inverting the configuration of a *trans* precursor.

4. EXPERIMENTATION

^1H and ^{13}C NMR spectra were obtained on a Bruker WM-250 spectrometer as solutions in $CDCl_3$ using TMS as the internal standard. Carbon signals were assigned by an INEPT pulse sequence. Purity was established in part by thin-layer chromatography (TLC) analyses that were performed with Analtech 2.5 by 10-cm, 259-mM analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel using Taber's[17] method. The Et_2O used for chromatographic separations was a commercial concentrate containing varying proportions of EtOH and other impurities that were necessary to ensure sufficient polarity for effective separations; anhydrous Et_2O is less polar and resulted in poor separations. Gas chromatography/mass spectrometry (GC/MS) analyses were performed on a Hewlett-Packard 5995 instrument.

4.1 1,2,3,6-Tetrahydropyridine (3).

Ferles' method[13] was modified as follows. Eight grams (210 mmol) of $LiAlH_4$ and 300 mL of dry Et_2O were added at room temperature to a flame-dried, 2-L, three-necked, round-bottom flask fitted with a mechanical stirrer, reflux condenser, and nitrogen inlet adapter.

Nine grams (68 mmol) of $AlCl_3$ in 159 mL of dry Et_2O followed by the dropwise addition of 10.92 mL of pyridine dissolved in 50 mL of Et_2O was added to this solution. The mixture was refluxed with stirring for 5 hr. Then the mixture was cooled to 0 °C and quenched by the cautious, sequential, dropwise addition of 10 mL of H_2O, 10 mL of 10% aqueous NaOH, and 20 mL of H_2O. The precipitated aluminum salts were separated by suction filtration and washed with 250 mL of Et_2O. The resulting filtrate was dried ($NaSO_4$) and concentrated on the rotary evaporator, while the bath temperature was maintained below 30 °C to prevent loss of product to provide 7.176 g (64%) of **3**, which was used without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.55 (br s, 1 H, NH), 2.07 (m, 2H, CH_2 at C_5), 2.98 (t, 2 H, CH_2 at C_6), 3.32 (br s, 2 H, CH_2 at C_2), 5.76 (m, 2 H, HC=CH).

4.2 1-(1,2,3,6-Tetrahydropyridinyl)phenylacetamide (4).

A mixture of 20.68 g (248.7 mmol) of **3** and 400 mL of dry toluene (distilled from CaH_2) was added to a 1-L, three-necked flask equipped with an addition funnel, mechanical stirrer, and nitrogen inlet adapter. A solution of 41.60 mL of triethylamine in 100 mL of toluene and 36.19 mL (42.31 g, 273.6 mmol) of phenylacetyl chloride was added sequentially dropwise. The reaction mixture was stirred at room temperature for 2 hr and then quenched with H_2O. The organic phase was washed with 10% HCl, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried ($NaSO_4$) and concentrated *in vacuo* to provide 50 g of crude product. Chromatography of 10.0 g of this material on silica gel (100 g) using 40% petroleum ether in ethyl acetate and collecting 100-mL fractions gave 5.39 g (54%) of **4**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 - 2.20 (m, 2 H), 3.43 - 4.11 (m, 6 H), 7.26 (m, 5 H).

4.3 1-(3,4-Epoxypiperidyl)phenylacetamide (5).

A solution of 20.71 g (102.9 mmol) of **4** in 100 mL of dry CH_2Cl_2 (distilled from CaH_2) was added to a 500-mL, round-bottom flask equipped with a rubber septum, a needle connected to nitrogen, and a magnetic stirring bar. The solution was cooled to 0 °C and then 24.42 g (80%, 113.2 mmol) was added portionwise. The solution was allowed to warm to room temperature and was stirred overnight. The resulting precipitate was removed by filtration and washed with 25 mL of CH_2Cl_2. The filtrate was passed through a pad of anhydrous K_2CO_3, washed with 100-mL of CH_2Cl_2, dried ($NaSO_4$), and concentrated *in vacuo*. The crude product was absorbed on 20 g of coarse silica gel and chromatographed on silica gel (100 g) using Et_2O, collecting 100-mL fractions. Fractions 3 and 4 gave 5.54 g (24.8%) of product containing traces of impurities, whereas fractions 5-9 gave 14.56 (65.1%) of pure **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.54 - 217 (m, 2 H), 3.24 (m, 4 H), 3.67 - 4.23 (m, 2 H), 7.34 (m, 5 H.)

4.4 Cleavage of Epoxide 5 with Aniline (6 and 7).

A mixture of 1.76 g (8.11 mmol) of **5**, 7.38 mL (7.52 g, 80.8 mmol) of aniline, 0.69 mL of H_2O, and 8.0 mL of DMF was refluxed with magnetic stirring under a nitrogen atmosphere for 4 hr. After cooling to room temperature, the solution was diluted with 20 mL of H_2O and extracted with 100 mL of Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was distilled using a bulb-to-bulb apparatus (bath, 55 °C; 0.2 mm Hg) to remove the excess aniline. Chromatography on 100 g of silica gel was effected using Et_2O, collecting 100-mL fractions. Fractions 5-7 provided 1.078 g of **7** as a tan solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 - 1.63 (m, 1 H), 1.92 (m, 1 H), 2.48 - 3.25 (m, 4 H), 3.56 (m, 2 H), 3.70 (m, 2 H), 3.86 - 4.65 (m, 2 H), 6.24 - 7.48 (m, 10 H); ^{13}C NMR

(250 MHz, $CDCl_3$) ppm 31.23, 31.41, 32.03, 39.54, 40.98, 43.95, 44.40, 48.15, 56.08, 56.18, 70.36, 70.66, 76.57, 77.08, 77.59, 113.15, 113.47, 118.05, 126.91, 128.25, 128.54, 128.79, 128.91, 129.40, 134.74, 134.84, 146.53, 146.97, 162.11, 169.76, 170.04; GC/MS *m/z* 310(M^+). Fraction 8 consisted of 0.438 g of a mixture of 6 and 7. Fractions 9-11 produced 0.767 g of 6 as a tan solid: ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 - 1.24 (m, 2 H), 2.04 (m, 1 H), 2.58 (m, 1 H), 2.92 (m, 1 H), 2.99 - 3.38 (m, 3 H), 3.44 - 3.76 (m, 3 H), 3.93 - 4.73 (m, 1 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 29.42, 30.09, 40.60, 40.86, 44.55, 46.61, 50.58, 56.72, 57.26, 69.46, 70.20, 76.66, 113.60, 113.72, 117.75, 117.93, 126.83, 128.48, 128.66, 129.21, 134.73, 134.85, 147.21, 169.86, 169.92. The combined yield of 6 and 7 was 90%.

4.5 1-(3-Oxo-4-phenylaminopiperidyl)phenylacetamide (8).

The following method is a modification of the method of Swern.[15] A solution of 0.074 mL (0.11 g, 0.852 mmol) of oxalyl chloride and 3 mL of dry CH_2Cl_2 was added into a flame-dried, 25-mL, round-bottom flask equipped with a rubber septum, a needle for maintaining a nitrogen atmosphere, and a magnetic stirring bar. The solution was cooled to -60 °C, and 0.121 mL (0.133 g, 1.70 mmol) of DMSO was added via syringe. The solution was stirred 2 min, and 0.240 g (0.774 mmol) of 6 dissolved in 4.7 mL of CH_2Cl_2 was added dropwise, via syringe over a 5-min period. After stirring at -60 to -50 °C for 15 min, 0.54 mL (0.39 g, 3.9 mmol) of triethylamine was added dropwise, and the solution was stirred for 20 min at -60 °C. The reaction mixture was treated with 20 mL of H_2O and 80 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried ($NaSO_4$), and concentrated *in vacuo*. The crude product was chromatographed with Et_2O on silica gel (10 g), collecting 10-mL fractions. Fractions 5-9 proved to be pure 8 (0.0957 g): ^1H NMR (250 MHz, $CDCl_3$) δ 2.31 - 2.63 (m, 2 H), 2.90 (m, 1 H), 3.71 (m, 1 H), 3.87 (m, 2 H), 4.13 (m, 1 H), 4.39 (m, 1 H), 4.85 (m, 1 H), 5.14 (dm, 1 H), 6.62 - 7.50 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 40.13, 40.31, 41.35, 42.29, 46.14, 47.83, 51.55, 60.20, 60.69, 76.54, 77.06, 112.74, 113.12, 118.38, 127.35, 127.44, 128.11, 128.51, 129.16, 129.32, 129.60, 134.38, 145.53, 145.84, 169.80, 170.23, 203.97, 204.25. Impure product was found in Fractions 4 and 10-13.

4.6 1-(4-Oxo-3-phenylaminopiperidyl)phenylacetamide (12).

Following the procedure described above for 8, regioisomeric 12 was prepared: ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 - 1.75 (m, 1 H), 2.41 - 2.73 (m, 2 H) 3.53 - 3.89 (m, 4 H), 3.78 (m, 2 H), 4.05 (m, 1 H), 4.26 (m, 1 H), 3.38 (s, 1 H), 6.43 - 7.43 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 40.12, 40.30, 41.05, 41.34, 42.29, 46.14, 47.85, 51.56, 60.22, 60.69, 76.51, 77.01, 77.52, 112.76, 113.12, 118.39, 126.73, 127.22, 127.41, 127.66, 128.11, 128.51, 128.75, 129.15, 129.30, 129.58, 134.37.

4.7 *trans*-1-(2-Phenylethyl)-3-hydroxy-4-phenylaminopiperidine (2) from Amide 6.

A mixture of 4.368 g (14.07 mmol) of 6 and 28 mL of dry THF was added to a 250-mL, round-bottom flask equipped with a Claisen adapter, magnetic stirring bar, and nitrogen inlet adapter. After cooling to -78 °C, 1.068 g (28.14 mmol) of $LiAlH_4$ was added in one portion. The cooling bath was removed, and the reaction mixture was allowed to warm and stirred at room temperature for 1 hr before cooling to 0 °C and quenching by the cautious, sequential addition of 1 mL of H_2O, 1 mL of 10% aqueous NaOH, and 2 mL of H_2O. The precipitated aluminum salts were separated by suction filtration and washed with 100 mL of Et_2O followed by 200 mL of acetone. The resulting filtrate and washes were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was chromatographed on silica gel

(100 g) with 3% EtOH in Et_2O, collecting 100-mL fractions. Fractions 4-7 gave 2.43 g of **2** contaminated with a small quantity of isopropanol formed by $LiAlH_4$ reduction of acetone. The acetone could be removed by repeating the chromatography or by bulb-to-bulb distillation (50 °C, 0.2 mm Hg.)

4.8 1-(*trans*-3-Hydroxy-4-N-phenylacetamidopiperidyl)-phenylacetamide (9).

A solution of 0.658 mL (0.724 g, 9.22 mmol) of acetyl chloride and 1.29 mL (0.937 g, 9.27 mmol) of triethylamine was added rapidly to a solution of 2.392 g (7.710 mmol) of **6** in 38 mL of dry toluene. The resulting solution was stirred at room temperature for 2 hr and quenched by dilution with H_2O. After separation of phases, the aqueous phase was extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was chr[illegible] on silica gel (100 g) using 2% EtOH in anhydrous Et_2O, collecting 100-mL f[illegible]s. Fractions 3-6 gave **9** (1.128 g, 55.3% based on consumed **6**): ^1H NMR (250 MHz, C[illegible]3) δ 1.11 - 1.49 (m, 2 H), 1.56 - 1.86 (m, 2 H), 2.02 (d, 3 H), 3.06 (m, 1 H), 3.36 (m, 3 H), 3[illegible]d, 2 H), 3.90 (m, 1 H), 4.14 (m, 1 H), 4.86 (br s, 1 H), 6.21 - 7.47 (m, 10 H); ^{13}C NMR (25[illegible] MHz, $CDCl_3$) ppm 15.25, 18.36, 20.95, 28.24, 28.50, 38.91, 40.93, 43.15, 44.09, 48.21, 52.81, 53.07, 57.85, 65.71, 70.80, 71.68, 76.83, 77.34, 77.86, 112.90, 117.65, 117.74, 126.93, 128.34, 128.52, 128.82, 128.92, 129.29, 129.47, 134.84, 146.28, 146.57, 169.72, 170.27, 170.73, 170.84. Fractions 8-16 contained 0.593 g of unreacted **6**.

4.9 1-[*trans*-3-[(Methylsulfonyl)oxy]-4-N-phenylacetamido-piperidyl] phenylacetamide (10).

To a solution of 1.128 g (3.201 mmol) of **9** in 16 mL of dry CH_2Cl_2 under a nitrogen atmosphere at -25 °C was added dropwise 4.46 mL (3.24 g, 32.0 mmol) of triethylamine followed by 1.239 mL (1.834 g, 16.00 mmol) of methanesulfonyl chloride. The resulting solution was stirred at -25 °C for 0.5 hr and at 0 °C for 0.5 hr, followed by neutralization with 10% HCl. After extraction with 100 mL of CH_2Cl_2, the organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude mesylate was chromatographed on silica gel (100 g) using 10% acetone in CH_2Cl_2, collecting 100-mL fractions. Fraction 4 contained a trace of **9**, whereas fractions 5-7 provided 1.246 g of **10** (90%) as white crystals: ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (m, 1 H), 1.58 (m, 1 H), 1.70 (s, 1 H), 2.14 (m, 3 H), 2.24 (s, 1 H), 3.28 (s, 3 H), 3.82 (m, 3 H), 4.32 (m, 1 H), 4.58 (m, 2 H), 7.16 - 7.56 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 21.24, 30.19, 30.70, 39.78, 40.41, 41.07, 42.29, 43.65, 44.48, 48.35, 58.03, 59.26, 66.86, 68.34, 70.43, 76.52, 77.03, 77.54, 77.83, 126.82, 126.99, 128.50, 128.77, 129.43, 130.17, 130.44, 132.35, 135.01, 170.02, 170.46.

4.10 cis-1-(3-Hydroxy-4-phenylaminopiperidyl)phenylacetamide (11).

To 1.246 g (2.894 mmol) of **10** in a 250-mL, round-bottom flask fitted with a reflux condenser and magnetic stirring bar was added 16.4 mL of 54% aqueous $N_2H_2 \cdot H_2O$. The resulting solution was stirred at room temperature for 5 min, warmed to 110 °C, and refluxed for 1.5 hr. After cooling to room temperature, 10 mL of brine and 100 mL of CH_2Cl_2 were added, and the organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed on 50 g of silica gel using 10% EtOH in Et_2O, collecting 75-mL fractions. Fractions 3 and 4 yielded 0.638 g of **11** and **6**. Fractions 5-7 provided 0.465 g of pure **11** as a glassy solid: ^1H NMR (250 MHz, $CDCl_3$) δ 1.97 (m, 3 H), 2.27 (m, 1 H), 2.66 (m, 1 H), 3.74 (m, 4 H), 3.96 (m, 1 H), 4.63 (m, 1 H), 4.93 (m, 1 H), 7.14 - 7.48 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 34.05, 40.57, 40.86, 41.55, 42.32, 42.58, 42.89,

44.19, 44.67, 48.76, 61.88, 62.95, 68.57, 68.79, 69.23, 69.66, 76.64, 76.96, 77.14, 77.66, 126.95, 127.28, 128.39, 128.63, 128.80, 128.85, 129.31, 129.82, 129.94, 131.89, 133.57, 133.69, 143.28, 134.58, 134.78. 146.55, 170.05, 170.24; GC/MS *m/z* 310 (M^+).

4.11 *cis*-1-(2-Phenylethyl)-3-hydroxy-4-phenylaminopiperidine (1).

To 1.246 g (2.894 mmol) of mesylate **12** in a 250-mL, round-bottom flask fitted with a reflux condenser and magnetic stirring bar was added 16.4 mL of 54% hydrazine hydrate. This solution was stirred at room temperature for 5 min and heated under reflux for 1.5 hr. After cooling to room temperature, 10 mL of brine and 100 mL of CH_2Cl_2 were added. The organic phase was separated, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel (50 g) with 10% EtOH in Et_2O gave 0.638 g of a mixture of isomers, followed by 0.465 g of pure **13** as a glassy white solid. To a solution of 0.158 g (4.18 mmol) of $LiAlH_4$ in dry THF under a nitrogen atmosphere at -78 °C was added dropwise 0.649 g (2.09 mmol) of **13** dissolved in 10 mL of THF. When the addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature (1 hr.) The mixture was then cooled to 0°C and quenched by the cautious addition of 0.15 mL of H_2O, 0.15 mL of 10% NaOH, and finally, 0.30 mL of H_2O. The precipitated aluminum salts were removed by filtration and washed with 100 mL each of Et_2O and acetone. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was chromatographed on silica gel (10 g) with 5% EtOH in Et_2O. The later fractions provided 0.111 g of pure **1** as white needles: ^1H NMR (250 MHz, $CDCl_3$) δ 1.55 (br s, 2 H), 1.66 - 1.99 (m, 5 H), 2.52 (m, 2 H), 2.63 - 2.87 (m, 4 H), 4.13 (td, J = 4 Hz, 2 H), 4.76 (dd, J = 15, 4 Hz), 7.06 - 7.43 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 34.0, 34.1, 42.4, 51.4, 56.7, 59.4, 63.4, 69.4, 69.6, 76.6, 77.1, 77.6, 126.2, 128.5, 128.7, 129.7, 129.9, 132.1, 140.2; GC/MS *m/z* 296 (M^+).

Repeated column elutions with acetone (200 mL), with $Et_2O/Et_2NH/EtOH$: 80/10/10 (200 mL), and finally with CH_2Cl_2/MeOH : 90/10 (200 mL) were required to remove the last traces of **1** (0.459 g, impure.)

4.12 *trans*-1-(2-Phenylethyl)-3-hydroxy-4-phenylaminopiperidine (2).

A mixture of 1.79 g of epoxide **5**, 7.38 mL of aniline, 0.69 mL of H_2O, and 8.0 mL of DMF was refluxed under nitrogen for 4 hr with magnetic stirring. After cooling to room temperature the solution was diluted with 20 mL of H_2O and extracted with Et_2O (100 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. A bulb-to-bulb distillation (bath 55 °C, 0.2 mm Hg) was used to remove excess aniline. Chromatography on silica gel (100 g) using Et_2O gave 0.767 g of **6** and 1.078 g of a mixture of **6** and **7**.

A solution of 4.368 g (14.07 mmol) of **6** in 28 mL of dry THF was added to a 250-mL, round-bottom flask fitted with a Claisen adapter, nitrogen inlet adapter, and magnetic stirring bar. The solution was cooled to -78 °C and 1.068 g (28.14 mmol) of $LiAlH_4$ was added in one portion. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 hr. The reaction mixture was worked up as described for **1**, and the crude product was chromatographed on silica gel (100 g) using 3% EtOH in Et_2O to afford 2.43 g of **2** after recrystallization from Et_2O; ^1H NMR (250 MHz, $CDCl_3$) δ 1.67 (m, 1 H), 1.95 (m, 2 H), 2.22 (br t, 1 H), 2.56 (t, 2 H), 2.75 (m, 4 H), 3.11 (br d, 1 H), 3.46 (br s, 2 H), 3.67 (br, 1 H), 6.62 - 7.41 (m, 10 H); ^{13}C NMR (250 MHz, $CDCl_3$) ppm 31.6, 33.6, 50.8, 56.0, 56.2, 59.8, 71.1, 76.5, 77.0, 77.5, 113.7, 118.1, 126.1, 128.4, 128.7, 129.4, 140.1, 147.1; GC/MS *m/z* 296 (M^+).

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